(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 699 665 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication.
06.03.1996 Bulletin 1996/10

(51) Int Cl.[6]: **C07D 233/14**, C07D 403/06, A61K 31/415

(21) Application number: **95303820.5**

(22) Date of filing: **05.06.1995**

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **10.06.1994 US 257966**

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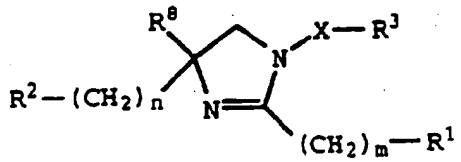
Remarks:
The applicant has subsequently filed a sequence listing and declared, that it includes no new matter

(54) Imidazoline derivatives, their preparation and their use as tachykinin receptor antagonists

(57) A compound of the formula



wherein:
m is 0 or 1;
n is 0 or 1;
X is $-(CHR^4)_p-(CHR^6)_q-$, where,
p is 0 or 1;
q is 0 or 1; and
R^4 and R^6 are independently selected from the group consisting of hydrogen and C_1-C_3 alkyl;
R^2 is phenyl, 2- or 3-indolyl, 2- or 3-indolinyl, benzothienyl, benzofuranyl, or naphthyl;

any one of which groups may be substituted with one or two moieties independently selected from the group consisting of halo, C_1-C_3 alkoxy, trifluoromethyl, C_1-C_4 alkyl, phenyl-C_1-C_3 alkoxy, and C_1-C_4 alkanoyl groups;
R^1 is hydrogen, trityl, phenyl, diphenylmethyl, phenoxy, phenylthio, hexamethyleneiminyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indolinyl, indolyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, tetrahydropyridinyl, reduced quinolinyl, reduced isoquinolinyl, phenyl-(C_1-C_6 alkylidenyl)-, phenyl-(C_1-C_4 alkoxy)-, quinolinyl-(C_1-C_6 alkylidenyl)-, isoquinolinyl-(C_1-C_6 alkylidenyl)-, reduced quinolinyl-(C_1-C_6 alkylidenyl)-, reduced isoquinolinyl-(C_1-C_6 alkylidenyl)-, benzoyl-(C_1-C_6 alkylidenyl)-, C_1-C_4 alkyl, or $-NH-CH_2-R^5$;

any one of which R^1 groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

or any one of which R^1 groups may be substituted with phenyl, piperazinyl, C_3-C_8 cycloalkyl, benzyl, C_1-C_4 alkyl, piperidinyl, pyridinyl, pyrimidinyl, C_2-C_6 alkanoylamino, pyrrolidinyl, C_2-C_6 alkanoyl, or C_1-C_4 alkoxycarbonyl;

any one of which groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, or C_2-C_4 alkanoylamino;
or R^1 is amino, a leaving group, hydrogen, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;
R^5 is pyridyl, anilino-(C_1-C_6 alkylidenyl)-, or anilinocarbonyl;
R^8 is hydrogen or C_1-C_6 alkyl; and
R^3 is phenyl, phenyl-(C_1-C_6 alkylidenyl)-, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_1-C_8 alkyl, naphthyl, C_2-C_8 alkenyl, or hydrogen;

any one of which groups except hydrogen may be substituted with one or two halo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, nitro, trifluoromethyl, or C_1-C_3 alkyl groups;
or a salt or solvate thereof.

This invention provides a novel series substituted 2-imidazolines which are useful in the treatment or prevention of a physiological disorder associated with an excess of tachykinins. This invention also provides methods for the treatment of such physiological disorders as well as pharmaceutical formulations which employ these novel compounds.

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Description

Tachykinins are a family of peptides which share the common amidated carboxy terminal sequence,

$$\text{Phe-Xaa-Gly-Leu-Met-NH}_2$$

hereinafter referred to as SEQ ID NO.1. Substance P was the first peptide of this family to be isolated, although its purification and the determination of its primary sequence did not occur until the early 1970's. Substance P has the following amino acid sequence,

$$\text{Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH}_2$$

hereinafter referred to as SEQ ID NO 2.

Between 1983 and 1984 several groups reported the isolation of two novel mammalian tachykinins, now termed neurokinin A (also known as substance K, neuromedin L, and neurokinin α), and neurokinin B (also known as neuromedin K and neurokinin β). See, J.E. Maggio, Peptides, 6 (Supplement 3) :237-243 (1985) for a review of these discoveries. Neurokinin A has the following amino acid sequence,

$$\text{His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH}_2$$

hereinafter referred to as SEQ ID NO:3. The structure of neurokinin B is the amino acid sequence,

$$\text{Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH}_2$$

hereinafter referred to as SEQ ID NO.4.

Tachykinins are widely distributed in both the central and peripheral nervous systems, are released from nerves, and exert a variety of biological actions, which, in most cases, depend upon activation of specific receptors expressed on the membrane of target cells. Tachykinins are also produced by a number of non-neural tissues.

The mammalian tachykinins substance P, neurokinin A, and neurokinin B act through three major receptor subtypes, denoted as NK-1, NK-2, and NK-3, respectively. These receptors are present in a variety of organs.

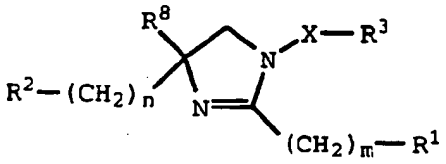
Substance P is believed inter alia to be involved in the neurotransmission of pain sensations, including the pain associated with migraine headaches and with arthritis. These peptides have also been implicated in gastrointestinal disorders and diseases of the gastrointestinal tract such as inflammatory bowel disease. Tachykinins have also been implicated as playing a role in numerous other maladies, as discussed infra.

In view of the wide number of clinical maladies associated with an excess of tachykinins, the development of tachykinin receptor antagonists will serve to control these clinical conditions. The earliest tachykinin receptor antagonists were peptide derivatives. These antagonists proved to be of limited pharmaceutical utility because of their metabolic instability.

Recent publications have described novel classes of non-peptidyl tachykinin receptor antagonists which generally have greater oral bioavailability and metabolic stability than the earlier classes of tachykinin receptor antagonists. Examples of such newer non-peptidyl tachykinin receptor antagonists are found in European Patent Publication 591,040 A1, published April 6, 1994; Patent Cooperation Treaty publication WO 94/01402, published January 20, 1994; Patent Cooperation Treaty publication WO 94/04494, published March 3, 1994; and Patent Cooperation Treaty publication WO 93/011609, published January 21, 1993.

In essence, this invention provides a class of potent non-peptide tachykinin receptor antagonists. By virtue of their non-peptide nature, the compounds of the present invention do not suffer from the shortcomings, in terms of metabolic instability, of known peptide-based tachykinin receptor antagonists.

This invention encompasses methods for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of Formula I



I

wherein

m is 0 or 1;

n is 0 or 1;

X is $-(CHR^4)_p-(CHR^6)_q-$, where,

p is 0 or 1;

q is 0 or 1; and

R^4 and R^6 are independently selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^2 is phenyl, 2- or 3-indolyl, 2- or 3-indolinyl, benzothienyl, benzofuranyl, or naphthyl;

any one of which groups may be substituted with one or two moieties independently selected from the group consisting of halo, C_1-C_3 alkoxy, trifluoromethyl, C_1-C_4 alkyl, phenyl-C_1-C_3 alkoxy, and C_1-C_4 alkanoyl groups;

R^1 is hydrogen, trityl, phenyl, diphenylmethyl, phenoxy, phenylthio, hexamethyleneiminyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indolinyl, indolyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, tetrahydropyridinyl, reduced quinolinyl, reduced isoquinolinyl, phenyl-(C_1-C_6 alkylidenyl)-, phenyl-(C_1-C_4 alkoxy)-, quinolinyl-(C_1-C_6 alkylidenyl)-, isoquinolinyl-(C_1-C_6 alkylidenyl)-, reduced quinolinyl-(C_1-C_6 alkylidenyl)-, reduced isoquinolinyl-(C_1-C_6 alkylidenyl)-, benzoyl-(C_1-C_6 alkylidenyl)-, C_1-C_4 alkyl, or $-NH-CH_2-R^5$;

any one of which R^1 groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

or any one of which R^1 groups may be substituted with phenyl, piperazinyl, C_3-C_8 cycloalkyl, benzyl, C_1-C_4 alkyl, piperidinyl, pyridinyl, pyrimidinyl, C_2-C_6 alkanoylamino, pyrrolidinyl, C_2-C_6 alkanoyl, or C_1-C_4 alkoxycarbonyl;

any one of which groups may be substituted with halo, C_1-C_4 alkyl, C_1-C_4 alkoxy, trifluoromethyl, amino, C_1-C_4 alkylamino, di(C_1-C_4 alkyl)amino, or C_2-C_4 alkanoylamino;

or R^1 is amino, a leaving group, hydrogen, C_1-C_4 alkylamino, or di(C_1-C_4 alkyl)amino;

R^5 is pyridyl, anilino-(C_1-C_6 alkylidenyl)-, or anilinocarbonyl;

R^8 is hydrogen or C_1-C_6 alkyl; and

R^3 is phenyl, phenyl-(C_1-C_6 alkylidenyl)-, C_3-C_8 cycloalkyl, C_5-C_8 cycloalkenyl, C_1-C_8 alkyl, naphthyl, C_2-C_8 alkenyl, or hydrogen;

any one of which groups except hydrogen may be substituted with one or two halo, C_1-C_3 alkoxy, C_1-C_3 alkylthio, nitro, trifluoromethyl, or C_1-C_3 alkyl groups;

or a pharmaceutically acceptable salt or solvate thereof.

In other embodiments this invention encompasses the novel compounds of Formula I and the salts and solvates of those compounds, as well as pharmaceutical formulations comprising at least one compound of Formula I, or a pharmaceutically acceptable salt or solvent of said compound, in combination with one or more pharmaceutically acceptable carrier, diluents, or excipients.

The terms and abbreviations used in the instant examples have their normal meanings unless otherwise designated. For example "°C" refers to degrees Celsius, "N" refers to normal or normality; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "ml" means milliliter or milliliters; "M" refers to molar or molarity; "MS" refers to mass spectrometry; "IR" refers to infrared spectroscopy; and "NMR" refers to nuclear magnetic resonance spectroscopy

As used herein, the term "C_1-C_6 alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl. The term "C_1-C_6 alkyl" includes within its definition the term "C_1-C_3 alkyl".

"C_1-C_6 alkylidenyl" refers to a straight or branched, divalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to, methylenyl, ethylenyl, propylenyl, isopropylenyl, butylenyl, isobutylenyl, t-butylenyl, pentylenyl, isopentylenyl, and hexylenyl.

"Halo" represents chloro, fluoro, bromo or iodo.

"C_1-C_6 alkylthio" represents a straight or branched alkyl chain having from one to six carbon atoms attached to a sulfur atom. Typical C_1-C_6 alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio and the like. The term "C_1-C_6 alkylthio" includes within its definition the term "C_1-C_3 alkylthio".

The term "C_2-C_8 alkenyl" as used herein represents a straight or branched, monovalent, unsaturated aliphatic chain having from two to eight carbon atoms Typical C_2-C_8 alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

"C_5-C_8 cycloalkenyl" represents a hydrocarbon ring structure containing from five to eight carbon atoms and having at least one double bond within that ring, which is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from halo, halo(C_1-C_4)alkyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, carboxy, C_1-C_4 alkoxycarbonyl, carbamoyl, N-(C_1-C_4) alkylcarbamoyl, amino, C_1-C_4 alkylamino, di(C_1-C_4)alkylamino or $-(CH_2)_a-R^c$ where a is 1, 2, 3 or 4 and R^c is hydroxy, C_1-C_4 alkoxy, carboxy, C_1-C_4 alkoxycarbonyl, amino, carbamoyl, C_1-C_4 alkylamino or di(C_1-C_4)alkylamino.

"C_1-C_6 alkylamino" represents a straight or branched alkylamino chain having from one to six carbon atoms attached to an amino group. Typical C_1-C_6 alkyl-amino groups include methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino and the like "C_1-C_6 alkylamino" encompasses within this term "C_1-C_4 alkylamino".

"Di(C_1-C_4 alkyl)amino" represents a straight or branched dialkylamino chain having two alkyl chains, each having

independently from one to four carbon atoms attached to a common amino group. Typical di(C_1-C_4)alkylamino groups include dimethylamino, ethylmethylamino, methylisopropylamino, *t*-butylisopropylamino, di-t-butylamino and the like

"C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *t*-butoxy, pentoxy and the like The term "C_1-C_6 alkoxy" includes within its definition the term "C_1-C_3 alkoxy".

"C_2-C_6 alkanoyl" represents a straight or branched alkyl chain having from one to five carbon atoms attached to a carbonyl moiety. Typical C_2-C_6 alkanoyl groups include ethanoyl, propanoyl, isopropanoyl, butanoyl, *t*-butanoyl, pentanoyl, hexanoyl, 3-methylpentanoyl and the like.

"C_1-C_4 alkoxycarbonyl" represents a straight or branched alkoxy chain having from one to four carbon atoms attached to a carbonyl moiety. Typical C_1-C_4 alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, *t*-butoxycarbonyl and the like.

"C_3-C_8 cycloalkyl" represents a saturated hydrocarbon ring structure containing from three to eight carbon atoms. Typical C_3-C_8 cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like

The term "amino-protecting group" as used in the specification refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups on the compound Examples of such amino-protecting groups include formyl, trityl, phthalimido, trichloroacetyl, chloroacetyl, bromoacetyl, iodoacetyl, and urethane-type blocking groups such as benzyloxycarbonyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-cyanobenzyloxycarbonyl, *t*-butoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)-prop-2-yloxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, fluorenylmethoxy-carbonyl ("FMOC"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxy)benzyloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl and the like; benzoylmethylsulfonyl group, 2-nitrophenylsulfenyl, diphenylphosphine oxide and like amino-protecting groups The species of amino-protecting group employed is usually not critical so long as the derivatized amino group is stable to the condition of subsequent reactions on other positions of the intermediate molecule and can be selectively removed at the appropriate point without disrupting the remainder of the molecule including any other amino-protecting groups. Preferred amino-protecting groups are trityl, *t*-butoxycarbonyl (*t*-BOC), allyloxycarbonyl and benzyloxycarbonyl. Further examples of groups referred to by the above terms are described by E. Haslam, "Protective Groups in Organic Chemistry", (J.G.W. McOmie, ed., 1973), at Chapter 2; and T.W. Greene and P G.M Wuts, "Protective Groups in Organic Synthesis" (1991), at Chapter 7.

The term "carboxy-protecting group" as used in the specification refers to substituents of the carboxy group commonly employed to block or protect the carboxy functionality while reacting other functional groups on the compound. Examples of such carboxy-protecting groups include methyl, *p*-nitrobenzyl, *p*-methylbenzyl, *p*-methoxy-benzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylene-dioxybenzyl, benzhydryl, 4,4-dimethoxy-benzhydryl, 2,2',4,4'-tetramethoxybenzhydryl, *t*-butyl, *t*-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylprop-2-yl, trimethylsilyl, *t*-butyldimethylsilyl, phenacyl, 2,2,2-trichloroethyl, 2-(di(n-butyl)methylsilyl)ethyl, *p*-toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)prop-1-en-3-yl and like moieties. Preferred carboxy-protecting groups are allyl, benzyl and *t*-butyl. Further examples of these groups are found in E. Haslam, supra, at Chapter 5, and T.W. Greene, et al., supra, at Chapter 5.

The term "leaving group" as used herein refers to a group of atoms that is displaced from a carbon atom by the attack of a nucleophile in a nucleophilic substitution reaction The term "leaving group" as used in this document encompasses, but is not limited to, activating groups.

The term "activating group" as used herein refers a leaving group which, when taken with the carbonyl (-C=O) group to which it is attached, is more likely to take part in an acylation reaction than would be the case if the group were not present, as in the free acid Such activating groups are well-known to those skilled in the art and may be, for example, succinimidoxy, phthalimidoxy, benzotriazolyloxy, benzenesulfonyloxy, methanesulfonyloxy, toluenesulfonyloxy, azido, or -O-CO-(C_4-C_7 alkyl).

The compounds used in the method of the present invention have multiple asymmetric centers. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All asymmetric forms, individual isomers and combinations thereof, are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center The term "R" (*rectus*) refers to that configuration of a chiral center with a clockwise relationship of group

priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" *(sinister)* refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

In addition to the (R)-(S) system, the older D-L system is also used in this document to denote absolute configuration, especially with reference to amino acids In this system a Fischer projection formula is oriented so that the number 1 carbon of the main chain is at the top. The prefix "D" is used to represent the absolute configuration of the isomer in which the functional (determining) group is on the right side of the carbon atom at the chiral center and "L", that of the isomer in which it is on the left.

As noted supra, this invention includes the pharmaceutically acceptable salts of the compounds defined by Formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

This invention further encompasses the pharmaceutically acceptable solvates of the compounds of Formulas I. Many of the Formula I compounds can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

The especially preferred methods of this invention are those methods employing compounds wherein

a) R^2 is substituted or unsubstituted 2- or 3-indolyl, phenyl, or naphthyl,

b) n is 1;

c) R^1 is hydrogen, phenyl, substituted phenyl, piperidinyl, substituted piperidinyl, piperazinyl, substituted piperazinyl, pyrrolidinyl, pyridyl, benzoyl, or morpholinyl;

d) R^3 is phenyl, substituted phenyl, C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkyl, naphthyl or substituted naphthyl; and

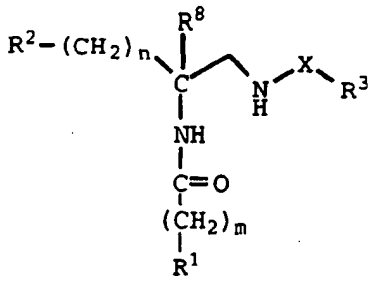
e) R^8 is hydrogen or methyl.

A most preferred group of compounds used in the methods of this invention are those of Formula I wherein R^2 is optionally substituted indolyl, R^1 is substituted piperidinyl or substituted piperazinyl, and R^8 is hydrogen or methyl. Another preferred group of compounds used in the methods of this invention are those of Formula I wherein R^2 is substituted

phenyl, R^1 is optionally substituted phenyl, substituted piperidinyl or substituted piperazinyl, and R^3 is phenyl or substituted phenyl

The compounds of the present invention can be prepared by a variety of procedures well known to those of ordinary skill in the art The particular order of steps required to produce the compounds of Formula I is dependent upon the particular compound being synthesized, the starting compound, and the relative lability of the substituted moieties.

An especially preferred process for preparing the compounds of Formula I is by the cyclization of a compound of Formula II.

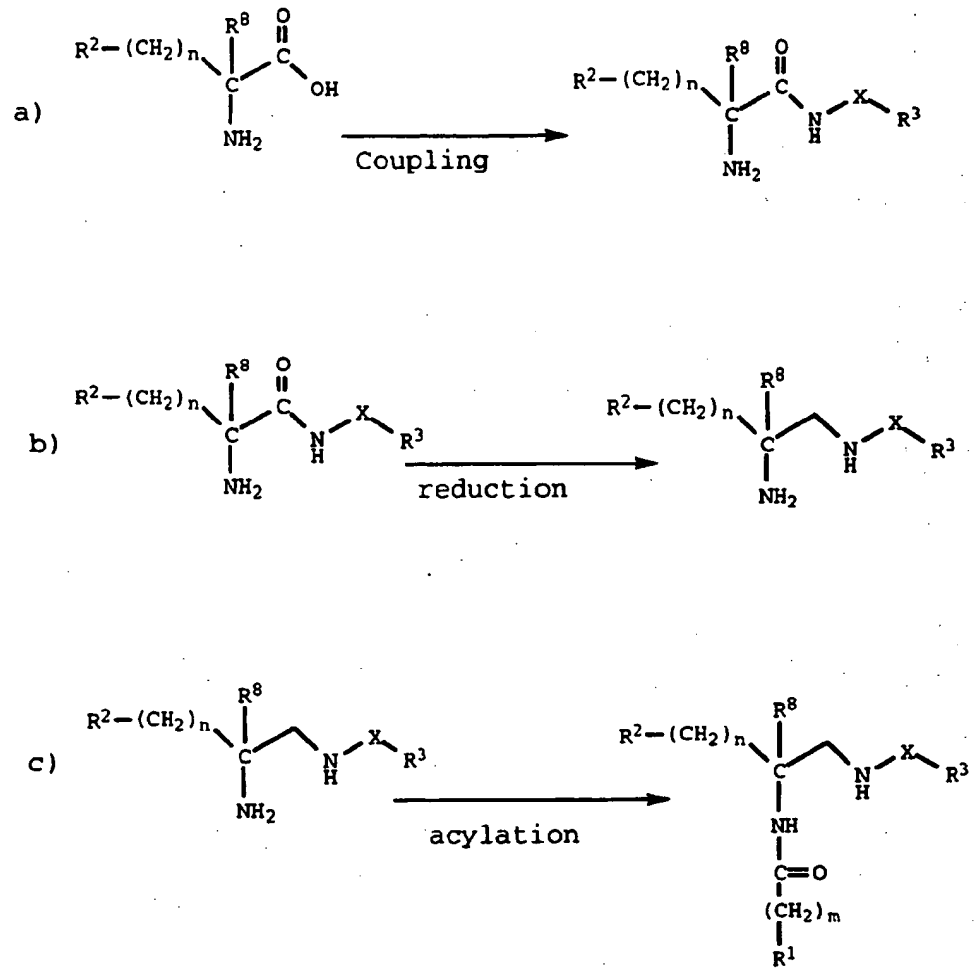


II

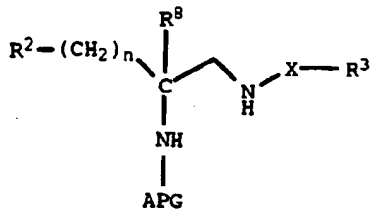
A preferred method of cyclizing a compound of Formula II employs heating a solution containing the compound of Formula II in a non-reactive solvent This dehydration reaction is preferably performed in a solvent having a suitably high boiling point, such as 1,2-dichlorobenzene.

The compounds of Formula II may be prepared by a variety of methods known to those of skill in the art. One such synthesis scheme is shown in the series of reactions depicted in Scheme I, infra.

Scheme I

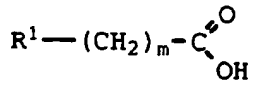


Another preferred method of synthesizing a compound of Formula I is by reacting a compound of Formula III



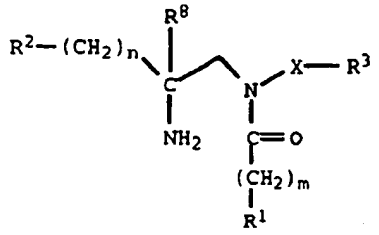
III

where APG is an acid-labile amino protecting group, with a carboxylic acid of Formula IV



IV

An especially preferred such acid is formic acid. The reaction of a compound of Formula III with a compound of Formula IV results in the formation of an intermediate of Formula V



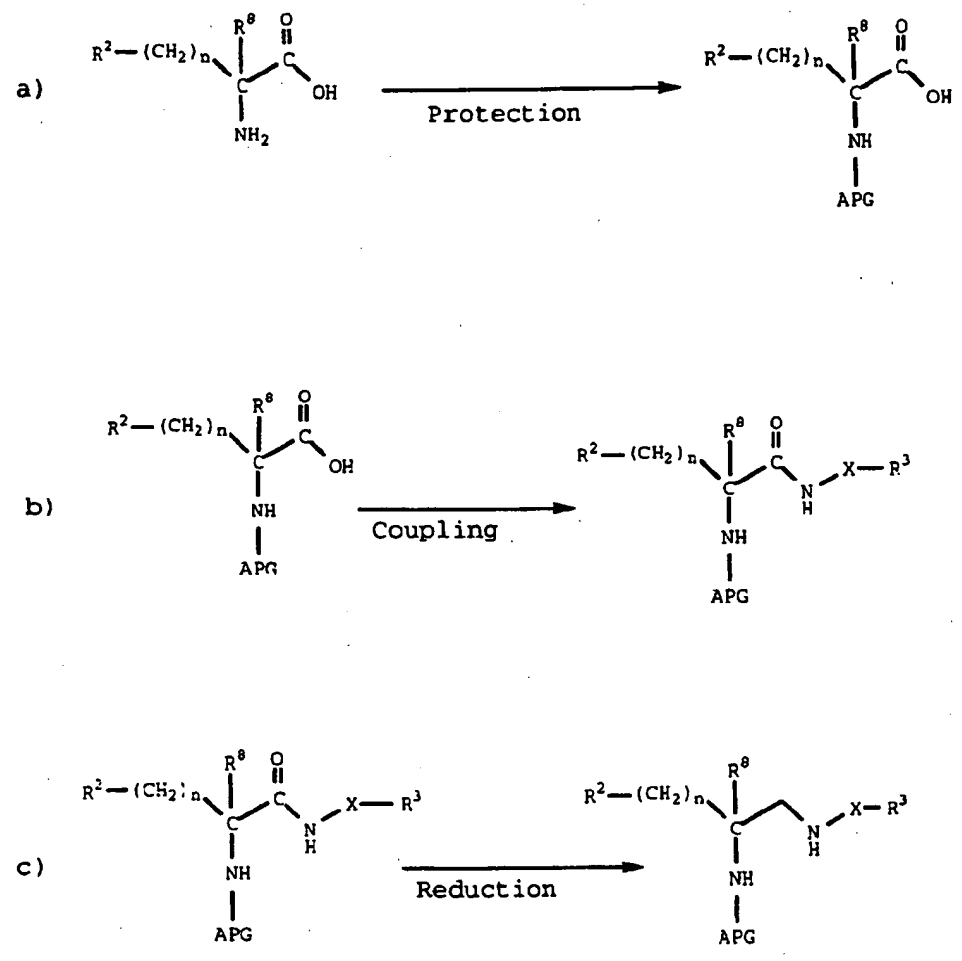
V

which may be isolated, but more preferably is not. The conversion of a compound of Formula III to a compound of Formula I proceeds most readily at temperatures greater than 20°C, more preferably at temperatures greater than 50°C. The reaction is performed in a non-reactive solvent which has a sufficiently high boiling temperature.

If it is desired to isolate the intermediate of Formula V, the reaction is performed at low temperature, preferably at reaction temperatures lower than 10°C, more preferably at temperatures below 0°C.

The compounds of Formula III may be prepared by a variety of methods known to those of skill in the art. One such synthesis scheme is depicted in Scheme II, infra.

Scheme II



The coupling of the substituted amine can be performed by many means known in the art, the particular methods employed being dependent upon the particular compound used as the starting material and the type of substituted amine used in the coupling reaction. These coupling reactions frequently employ commonly used coupling reagents such as 1,1-carbonyl diimidazole, dicyclohexylcarbodiimide, diethyl azodicarboxylate, 1-hydroxybenzotriazole, alkyl chloroformate and triethylamine, phenyldichlorophosphate, and chlorosulfonyl isocyanate. Examples of these methods are described infra.

The intermediate amides are reduced to amines using procedures well known in the art. These reductions can be performed using lithium aluminum hydride as well as by use of many other different aluminum-based hydrides. An especially preferred reagent employed in this reduction is RED-AL®. which is the tradename of a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene. Alternatively, the amides can be reduced by catalytic hydrogenation, though high temperatures and pressures are usually required for this. Sodium borohydride in combination with other reagents may be used to reduce the amide. Borane complexes, such as a borane dimethylsulfide complex, are especially useful in this reduction reaction.

The next step in Scheme I is the selective acylation of the primary amine using standard methods Because of the higher steric demand of the secondary amine, the primary amine is readily available for selective substitution.

This acylation can be done using any of a large number of techniques regularly employed by those skilled in organic chemistry One such reaction scheme is a substitution using an anhydride such as acetic anhydride. Another reaction scheme often employed to acylate a primary amine employs a carboxylic acid preferably with an activating agent. An amino-de-alkoxylation type of reaction uses esters as a means of acylating the primary amine. Activated esters which are attenuated to provide enhanced selectivity are very efficient acylating agents. One preferred such activated ester is *p*-nitrophenyl ester, such as p-nitrophenyl acetate.

Primary amines can also be acylated using amides to perform what is essentially an exchange reaction. This reaction is usually carried out with the salt of the amine. Boron trifluoride, usually in the form of a boron trifluoride diethyl ether complex, is frequently added to this reaction to complex with the leaving ammonia

In order to preferentially prepare one optical isomer over its enantiomer, the skilled practitioner can proceed by one of two routes. The practitioner may first prepare the mixture of enantiomers and then separate the two enantiomers. A commonly employed method for the resolution of the racemic mixture (or mixture of enantiomers) into the individual enantiomers is to first convert the enantiomers to diastereomers by way of forming a salt with an optically active salt or base These diastereomers can then be separated using differential solubility, fractional crystallization, chromatography, or like methods. Further details regarding resolution of enantiomeric mixtures can be found in J Jacques, et al., "Enantiomers, Racemates, and Resolutions", (1991).

In addition to the schemes described above, the practitioner of this invention may also choose an enantiospecific protocol for the preparation of the compounds of Formula I. Such a protocol employs a synthetic reaction design which maintains the chiral center present in the starting material in a desired orientation These reaction schemes usually produce compounds in which greater than 95 percent of the title product is the desired enantiomer.

Typical reaction conditions for reach of these reactions are described in the preparations and examples infra.

Preparation 1

Preparation of (RS)-1-phenyl-1-(tritylamino)-[N-(2-methoxybenzyl)acetylamino]ethane

To a stirring solution of α-aminophenylacetic acid (15.0 g, 99.2 mmol) in 430 ml of methylene chloride was added trimethylsilyl chloride (13.8 ml, 109.12 mmol) dropwise. The resulting mixture was stirred for about ninety minutes, followed by the dropwise addition of triethylamine (30.4 ml, 218.24 mmol). The resulting mixture was then stirred for about thirty minutes after which trityl chloride (30.4 g, 109.12 mmol), dissolved in 50 ml of methylene chloride, was added The progress of the reaction was monitored by thin layer chromatography

After the reaction mixture was stirred overnight, the mixture was concentrated in vacuo. The concentrate was then partitioned between 5% citric acid and a 1:1 mixture of ethyl acetate and dietyl ether. The aqueous fraction was then extracted with a 1.1 mixture of ethyl acetate and diethyl ether.

The organic fractions were then combined, washed twice with brine, and then dried over sodium sulfate. The solvents were removed in vacuo and the residue was then dissolved in boiling ethyl acetate and then filtered. The solvents were again removed in vacuo and the resulting α-(tritylamino)phenylacetic acid was recrystallized from boiling ethyl acetate with hexanes added. (Yield: 30.82 g, 79%).

To a stirring solution of α-(tritylamino)phenylacetic acid (19.32 g, 49 mmol) in 650 ml of tetrahydrofuran, 2-methoxybenzylamine (6.72 ml, 49 mmol) was added dropwise, followed by the addition of hydroxybenztriazole hydrate (6.62 g, 49 mmol) and triethylamine (6.83 ml, 49 mmol). The resulting mixture was cooled to 0°C and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (9.39 g, 49 mmol) was added, followed by the addition of 400 ml of tetrahydrofuran.

The resulting solution was warmed to room temperature. The progress of the reaction was monitored by thin layer

chromatography. After the solution was stirred overnight, the solvents were removed in vacuo. The residue was then dissolved in methylene chloride, washed twice with sodium carbonate, followed by two washings with brine The organic fraction was then dried over sodium sulfate, and the solvents were removed in vacuo. The resulting intermediate, N-(2-methoxybenzyl)-1-phenyl-1-tritylamino-acetamide (18.81 g, 75%) was recrystallized from boiling ethyl acetate/hexanes

The N-(2-methoxybenzyl)-1-phenyl-1-(tritylamino)acetamide (18.85 g, 36.6 mmol) was dissolved in 120 ml of tetrahydrofuran and then brought to reflux RED-AL® [a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene] (48 ml, 164.7 mmol) was dissolved in 120 ml of tetrahydrofuran and then added dropwise to the N-(2-methoxybenzyl)-1-phenyl-1-tritylamino-acetamide/tetrahydrofuran solution. The solution was refluxed and the progress of the reaction was monitored by thin layer chromatography.

After the solution was refluxed overnight, the reaction solution was then cooled to room temperature and the reaction was quenched with a saturated Rochelle's salt solution. The resulting mixture was then extracted with ethyl acetate.

The organic fraction was then washed twice with sodium carbonate, twice with brine, and then dried over sodium sulfate The solvents were then removed in vacuo to yield the intermediate N-(2-methoxybenzyl)-1-phenyl-1-(tritylamino) ethylamine (17.3 g, 95%).

The N-(2-methoxybenzyl)-1-phenyl-1-(tritylamino)ethylamine (16.87 g, 33.8 mmol) was then dissolved in 100 ml of tetrahydrofuran. The resulting solution was cooled to 0°C and then triethylamine (5.65 ml, 40.6 mmol) was added, followed the addition of acetic anhydride (3 8 ml, 40.6 mmol).

The reaction mixture was then warmed to room temperature and then stirred overnight. The progress of the reaction was monitored by thin layer chromatography The solvents were then removed in vacuo and the residue was disolved in methylene chloride, washed twice with water, then twice with brine, and then dried over sodium sulfate. The solvents were then removed in vacuo and the residue was washed with boiling diethyl ether to yield the intermediate 1-phenyl-1-(tritylamino)-[N-(2-methoxybenzyl)acetylamino]ethane (16.27 g, 70%). FDMS 540 (M^+).

^{1}H NMR ($CDCl_3$) δ 2:1 mixture of amide rotamers 1.9 (s, 2/3 • 3H), 1.96 (s, 1/3 • 3H), 2.93 (m, 1H), 3 05 (m, 1H), 3.67 (s, 2/3 • 3H), 3.75 (s, 1/3 • 3H), 3.75 (m, 1H), 3.93 (d, J=18 Hz , 2H), 4.21 (ABq J=14 Hz, Δν=21 Hz, 1H), 6.66-6.90 (m, 3H), 6.90-7.35 (m, 15H), 7 35-7.55 (m, 6H)

Analysis for $C_{37}H_{36}N_2O_2$:			
Theory:	C, 82 19;	H, 6 71;	N, 5.18.
Found	C, 82.37,	H, 6.69;	N, 5.03.

Preparation 2

(RS)-2-amino-2-methyl-1-[N-(2-methoxybenzyl)amino]-3-(1H-indol-3-yl)propane

In a 500 ml round-bottom flask under a nitrogen atmosphere, α-methyltryptophan (5.0 g, 22.9 mmol) was slurried in 300 ml of dry tetrahydrofuran. While stirring the reaction mixture 2-methoxybenzylamine (3 ml, 22 9 mmol) was added, followed by the addition of hydroxybenztriazole hydrate (3.15 g, 22.9 mmol) and triethylamine (3.25 ml, 22.9 mmol). The resulting mixture was cooled to 0°C and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.5 g, 22.9 mmol) was added

The reaction mixture was then slowly warmed to room temperature and was stirred while the progress of the reaction was monitored by thin layer chromatography. After stirring overnight, the reaction mixture was concentrated in vacuo, dissolved in ethyl acetate, and then washed twice with a saturated sodium bicarbonate solution, followed by two washings with brine The organic fraction was then dried over sodium sulfate and the solvents were removed in vacuo. The desired intermediate, N-(2-methoxybenzyl)-2-methyl-2-amino-1-(lH-indol-3-yl)-3-propionamide, was further purified by chromatography. (Yield: 4.57 g, 60%).

The N-(2-methoxybenzyl)-2-methyl-2-amino-1-(1H-indol-3-yl)-3-propionamide (2.25 g, 6.68 mmol) was dissolved in 15 ml of tetrahydrofuran under a nitrogen atmosphere. The resulting solution was warmed to 80°C. RED-AL® [a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene] (8.8 ml, 30.06 mmol) was dissolved in 3.7 ml of tetrahydrofuran and then added dropwise to the reaction mixture. The solution was then warmed to 80°C and the progress of the reaction was monitored by thin layer chromatography.

After the solution was maintained at 80°C for about 23 hours, the reaction solution was then cooled to room temperature and the reaction was quenched with a saturated Rochelle's salt solution The resulting mixture was then extracted twice with ethyl acetate The organic fraction was washed twice with brine and then dried over sodium sulfate. The solvents were removed in vacuo The desired (RS)-2-amino-2-methyl-1-[N-(2-methoxybenzyl)amino]-3-(1H-indol-3-yl)propane was further purified by chromatography (1.3 g, 60%).

FDMS 323 (M^+)

^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 2.60 (s, 2H), 2 74 (br s, 3H), 2.90 (d, J=8 Hz, 2H), 3.80 (s, 3H), 3.87 (s, 2H), 6.83-6.95